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(54) LIQUID PHARMACEUTICAL COMPOSITION FOR ORAL ADMINISTRATION OF BITTER HYDROLYSIS-SUSCEPTIBLE ACTIVE SUBSTANCES

(57) Liquid pharmaceutical composition for the oral administration of active substances that are bitter and susceptible to hydrolysis.

The composition (for 100 ml) comprises: 3-15 g of active substance; 0.01-0.3 g of preservative (sorbic acid, methyl p-hydroxybenzoate); sufficient amount of an edible oily vehicle formed by triglycerides of short- or medium-chain acids (caprylic, capric) to make up 100 ml; a suitable quantity of sweetener (sodium saccharin, sodium cyclamate, ammonium glycyrricinate) optionally accompanied by a suitable amount of a flavouring agent (walnut, condensed milk, coconut, banana); 0.5-2 g of soya lecithin; 0.1-5 g of thickener of the type derived from cellulose (N-ethylcellulose); and 0.05-1 g of a polysorbate type surfactant. Optionally it includes 0.5-5 g of mannitol and 1-5 g of sodium bicarbonate. It is useful for the administration of bitter active substances (ciprofloxacin, paracetamol, erythromycin etc.) in children, the elderly and patients who are little motivated. It is stable, easy to ingest and of bearable taste.

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Description

[0001] This invention refers to the area of techniques for pharmaceutical or galenic compositions or formulations, in particular, for oral administration - not of the extemporaneous type, but of the ready-to-use type - of active pharmaceutical substances that have a bitter or disagreeable taste, and that cannot be in contact with water for a long time as they are susceptible to decomposition via hydrolysis

BACKGROUND ART

[0002] In modern therapeutics, oral administration forms are more desirable than parenteral or rectal administration forms, amongst other reasons because they tend to provoke less rejection in the patients. Amongst the oral forms, the solid forms (tablets, capsules, pills, etc.,) are the most common ones; but their ingestion is often problematic for patients who are little motivated or have difficulties swallowing. Typically, amongst these patients are children, the elderly and those affected with disabilities or acute pain. In these cases, the liquid oral forms, in particular those of ready-to-use type (syrups, elixirs, drops, etc.,) are particularly desirable.

[0003] But the liquid oral forms encounter problems when the active substance has a disagreeable taste and/or is unstable in long term contact with water. Also, it is important that the exterior appearance of the composition is homogeneous, therefore the main vehicles of the composition have to be capable of dissolving or suspending all its components, Thus, the masking of the taste, the stability and the good dissolution or suspension in the pharmaceutical forms that are liquid and oral, are technical problems to which considerable research and development efforts are currently being directed.

[0004] Amongst the liquid formulations proposed in the art for masking the taste of bitter active substances are to be found the suspensions that involve a great amount of sucrose and ingredients included in tablets (starch, lactose, magnesium stearate, etc.,); but these suspensions are usually disagreeable and have to be administered via gastric or nasogastric tubes. In the application WO 9534276 the use of propyleneglycol and sorbitol are proposed for masking the bad taste of some bitter active substances, such as thymol. In order to mask the bad taste of other active substances, such as gabapentin and tacrine, in application WO 9214443-A1 oil-in-water emulsions of microspheres containing the active substance are proposed. But the cited compositions contain water, thus, although useful for extemporaneous suspensions, they are not suitable for ready-to-use suspensions of active substances that are susceptible to decomposition by hydrolysis. In application ES 2105970-A1 it is proposed to mask the bad taste of ciprofloxacin by the addition of large quantities (around 15 %) of cocoa powder, which implies all the problems and limitations inherent in the ingestion of chocolate. Thus, in summary, the problem of oral administration, in liquid form, of active substances that are bitter and susceptible to hydrolysis has not yet been solved satisfactorily.

SUMMARY OF THE INVENTION

[0005] The present invention resolves the aforementioned problems by providing a new liquid non aqueous pharmaceutical composition for ready-to-use type oral administration, stable and with improved organoleptic characteristics, which, for every 100 ml, approximately comprises:

- between 3 and 15 g of active substance;
- between 0.01 and 0.3 g of a preservative selected from the group consisting of methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, propyl p-hydroxybenzoate, butylhydroxyanisole, butylhydroxytoluene, sorbic acid and their mixtures;
- sufficient amount of an edible oily vehicle formed by of triglycerides of short- or medium-chain acids for making up the 100 ml;
- a suitable amount of sweetener, optionally accompanied by a suitable amount of flavoring agent;
- between 0.5 and 2 g of soya lecithin;
- between 0.1 and 5 g of a thickener of the type derived from cellulose; and
- between 0.05 and 1 g of a surfactant of the polysorbate type.

[0006] The presence of lecithin, incorporated as illustated in the examples, allows an initial masking of the taste of the active substance, but at the same time acts as an anti-agglomeration agent, facilitating redispersion, and as an emulsifier, improving the speed of dissolution of the active substance and, therefore, its bioavailability.

[0007] The derivative of cellulose provides the appropriate viscosity in order to avoid the rapid sedimentation of the incorporated powders, but at the same time contributes to very effectively masking the taste of the active substance, also providing an agreeable and ideal texture for this type of suspension. The special technology for its addition, illustrated in the examples, is important for achieving its efficiency. In a preferred embodiment of the invention, the thickener

derived from cellulose is N-ethylcellulose.

[0008] The surfactant of polysorbate type favours the speed of dissolution of the composition and, in consequence, the bioavailability of the active substance. In a preferred embodiment, the surfactant of polysorbate type is selected from polysorbate-20, polysorbate-80 and their mixtures.

[0009] The edible oily vehicle made up of the triglycerides of short- or medium-chain acids, with a water content lower than 0.5 %, allows the dispersion of a relatively high amount of active substance, at the same time avoiding the phenomena of hydrolysis that occur in the aqueous suspensions. In a preferred embodiment of the invention, the edible oily vehicle made up of the triglycerides of short or medium chain acids is substantially composed of triglycerides of caprylic acid, capric acid or of their mixtures. The preservative guarantees the physico-chemical stability and avoids the microbiological contamination of the composition.

[0010] The presence of the sweetener, optionally accompanied by the flavoring agent, finishes off the masking of the repugnant taste of the active substance, in a way that is perfectly bearable to the palate. In a preferred embodiment of the invention, the appropriate amount of sweetener is selected from: 0.01-0.2 g of sodium saccharin, 0.1-5 g of sodium cyclamate, 0.1-2 g of ammonium glycyrricinate and their mixtures. In a particular embodiment, the appropriate amount of flavoring agent is selected from 0.1 and 1.0 g of one or various of the following flavours: walnut, condensed milk, coconut and banana.

[0011] In a particularly preferred embodiment, the composition also contains 0.5-5 g of mannitol, that apparently helps the solubility of the composition in the stomach.

[0012] In another particularly preferred embodiment, the composition also contains 1-5 g of sodium bicarbonate which, upon reacting with the acid medium of the stomach and forming carbon dioxide, causes an effervescence that facilitates the release of the active substance and its posterior dissolution.

[0013] In preferred embodiments of the present invention, illustrated in the enclosed examples, the active substance is selected from the group formed by ciprofloxacin, paracetamol and erythromycin. The composition with ciprofloxacin is especially preferred.

[0014] The compositions of the present invention prove to be surprisingly stable for long periods of time, which permits their use as a suspension for ready-to-use administration, whose advantages with respect to extemporaneous administration are well known.

[0015] The oily suspension of the invention provides a good bioavailability of the active substance, which translates into a high efficiency shortly after administration. As the taste proves to be acceptable, its administration is advantageous with respect to the known solid forms, especially in children and patients with little motivation.

DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT

[0016] The following examples illustrate the invention for the particular cases of three active substances of disagreeable taste, namely: ciprofloxacin, paracetamol and erythromycin. The final amount of water in all the compositions is of less than 0.5 %.

Example 1: General preparation process of the liquid compositions

[0017] For preparing a total amount of 100 ml of suspension, the following operations are followed:

a) Coating of the bitter active substance (between 3 and 15 g) with a concentrated lecithin solution (from 0.5 to 2 g of dry residue).

b) Drying (between 35°C and 45°C) and granulation.

c) Pulverisation of the granules obtained in (b), to a particle size of between 150 and 250 micras.

d) Coating of the powder obtained in (c) with mannitol (0.1-0.5 g) and polysorbate 20, polysorbate 80 or their mixtures (0.1-0.5 g).

e) Drying (between 35°C and 45°C) and granulation.

f) Pulverisation of the granules obtained in (e), to a particle size of between 100 and 150 micras.

g) Addition, under continuous stirring, of N-ethylcellulose (1 to 5 g) to a substantial part of the total volume of the mixture of triglycerides of short- and medium-chain acids, previously heating slightly above 100°C.

h) Cooling to 35-40°C of the mixture obtained in (g), and addition, with continuous stirring, of the powder obtained in (f).

i) Optional addition, with continuous stirring, of the sodium bicarbonate (1-5 g).

j) Addition, with continuous stirring, of the preservative (sorbic acid, methyl or ethyl p-hydroxybenzoate, butylhydroxyanisol, butylhydroxytoluene; 0.1- 0.8 g).

k) Standing (e.g. 10-18 h).

l) Addition, with continuous stirring, of the sweetener (sodium cyclamate, sodium saccharin, ammonium glycyrricinate, etc.; 0.1-5 g).

m) Addition, with continuous stirring, of the flavoring agent (walnut flavouring, condensed milk flavouring, coconut flavouring, banana flavouring etc; 0.1-0.5 g).

n) Addition, with continuous stirring, of the remaining volume of the triglycerides of short- and medium-chain acids in order to complete the 100 ml of suspension.

Example 2: Liquid composition of milk and walnut flavoured ciprofloxacin

[0018] Following the general technique described in Example 1, various suspensions of ciprofloxacin were prepared with the compositions indicated (amounts in grams per 100 ml), which obtained a good organoleptic acceptation in tests on healthy volunteers:

Ciprofloxacin	5-15
Soya lecithin	0.5-2.0
Mannitol	0.5-5.0
Polysorbate 20	0.05-1.0
Ethylcellulose N-50	0.1-5.0
Ammonium glycyrricinate	0.1-2.0
Sodium cyclamate	0.1-5.0
Sodium saccharin	0.01-0.2
Sorbic acid	0.01-0.3
Walnut flavouring	0.1-0.5
Condensed milk flavouring	0.1-0.5
Sodium bicarbonate	1-5
Medium chain triglycerides (Estasan™3775)	q.s. 100 ml

Example 3: Liquid composition of banana flavoured ciprofloxacin

[0019] Following the general technique described in Example 1, various suspensions of ciprofloxacin were prepared with the compositions indicated (amounts in grams per 100 ml), which obtained a good organoleptic acceptation in tests on healthy volunteers:

Ciprofloxacin	5-15
Soya lecithin	0.5-2.0
Polysorbate 80	0.05-1.0
Ethylcellulose N-30	0.1-5.0
Ammonium glycyrricinate	0.1-2.0
Methyl p-hydroxybenzoate	0.01-0.3
Banana flavouring	0.1-0.5
Medium chain triglycerides (Estasan™3775)	q.s. 100 ml

Example 4: Liquid composition of banana flavoured paracetamol

[0020] Following the general technique described in Example 1, various suspensions of paracetamol were prepared with the compositions indicated (amounts in grams per 100 ml), which obtained a good organoleptic acceptation in tests on healthy volunteers:

Paracetamol	5-10
Soya lecithin	0.5-2.0
Mannitol	0.5-2.0
Polysorbate 20	0.05-1.0
Ethylcellulose N-50	0.1-5.0
Sodium cyclamate	0,1-5,0
Sorbic acid	0.01-0.3
Banana flavouring	0.1-0.5
Medium chain triglycerides (Estasan™3775)	q.s. 100 ml

Example 5: Liquid composition of milk flavoured erythromycin

[0021] Following the general technique described in Example 1, various suspensions of erythromycin were prepared with the compositions indicated (quantities in grams per 100 ml), which obtained a good organoleptic acceptation in tests on healthy volunteers:

Erythromycin	3-6
Soya lecithin	0.5-2.0
Polysorbate 80	0.05-1.0
Ethylcellulose N-50	0.1-5.0
Sodium cyclamate	0.1-5.0
Sorbic acid	0.01-0.3
Condensed milk flavouring	0.1-0.5
Sodium bicarbonate	1-5
Medium chain triglycerides (Estasan™3775)	q.s. 100 ml

Claims

1. Liquid non-aqueous pharmaceutical composition for ready-to-use type administration, stable and with improved organoleptic characteristics, which, per 100 ml, contain: between 3 and 15 g of active substance; between 0.01 and 0.3 g of a preservative selected from the group consisting of methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, propyl p-hydroxybenzoate, butylhydroxyanisole, butylhydroxytoluene, sorbic acid and their mixtures; between 0.5 and 2 g of soya lecithin; between 0.1 and 5 g of a thickener of the type derived from cellulose; between 0.05 and 1 g of a polysorbate type surfactant; a suitable amount of sweetener, optionally accompanied by a suitable amount of flavoring agent; and sufficient amount of an edible oily vehicle formed by of triglycerides of short- or medium-chain acids for making up the 100 ml.

2. Composition according to claim 1, wherein the thickener derived from cellulose is N-ethylcellulose.

3. Composition according to any of the preceding claims, wherein the polysorbate type surfactant is selected from polysorbate-20, polysorbate-80, and their mixtures.

4. Composition according to any of the preceding claims, wherein the edible oily vehicle made up of triglycerides of short- or medium-chain acids is substantially composed of triglycerides of caprylic acid, of capric acid, or of their mixtures.

5. Composition according to any of the preceding claims, wherein the appropriate amount of sweetener is selected from: 0.01-0.2 g of sodium saccharin, 0.1-5 g of sodium cyclamate, 0.1-2 g of ammonium glycyrricinate, and their mixtures.

6. Composition according to any of the preceding claims, where the appropriate amount of flavoring agent is selected from 0.1 and 1.0 g of one or various of the following flavours: walnut, condensed milk, coconut and banana.

7. Composition according to any of the preceding claims, which further includes 0.5-5 g of mannitol.

8. Composition according to any of the preceding claims, which further includes 1-5 g of sodium bicarbonate.

9. Composition according to any of the preceding claims, wherein the active substance is selected from the group consisting of ciprofloxacin, paracetamol and erythromycin.

10. Composition according to any of the preceding claims, wherein the active substance is ciprofloxacin.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/ ES 00/00206

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K 47/44, 31/495, 31/165, 31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CIBEPAT, EPODOC, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 9204893 A (SMITH-KLINE BEECHAM CORPORATION) 2 April 1992 (02.04.92) ; the whole document.	1-10
Y	EP 750849 A (KAO CORPORATION) 2 January 1997 (02.01.97) ; Page 1, line 55 – page 5, line 40, tables 1 and 2, examples.	1-10
Y	ES 2105970 B (LABORATORIOS S.A.L.V.A.T., S.A.) 16 October 1997 (16.10.97) ; the whole document.	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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Date of the actual completion of the international search	Date of mailing of the international search report
31 July 2000 (31.07.00)	18 August 2000 (18.08.00)
Name and mailing address of the ISA/	Authorized officer
Facsimile No. S.P.T.O.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT
Information on patent family membefs

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PCT/ ES 00/00206

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